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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Dr. Quach is an Associate Professor of Gastroenterology at the University of Medicine and Pharmacy at Hochiminh City, Viet Nam, where he received his MD in 1997 and his PhD in 2011. Dr. Quach has published more than 100 reviews and original papers in local and international journals. He has received several awards, including Outstanding Presentation at the Biannual Scientific Congress of Vietnamese Nationwide Medical Schools, Medal of Creativeness from the Vietnamese Central Youth League, etc. Currently, he serves as a Vice President of the Vietnam Association of Gastroenterology and Secretary General of the Vietnam Federation for Digestive Endoscopy. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

*WJCC* mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for *WJCC* as 1.013; IF without journal self cites: 0.991; Ranking: 120 among 165 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2019 is 0.3 and Scopus CiteScore rank 2019: General Medicine is 394/529.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Ji-Hong Liu; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lei Wang.
Efficacy of afatinib in a patient with rare EGFR (G724S/R776H) mutations and amplification in lung adenocarcinoma: A case report

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Author contributions: He SY and Shen D contributed to the study concept and design and performed the statistical analysis; Lin QF, Chen J, and Yu GP contributed to the acquisition, analysis, or interpretation of the data; Zhang JL contributed to the drafting of the manuscript; Zhang J and Shen D contributed to the critical revision of the manuscript for important intellectual content.

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Conflict-of-interest statement: Zhang JL is an employee of Shanghai 3D Medicines Inc. All other authors declare no competing interests.

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Abstract

BACKGROUND
The most common EGFR mutations are in-frame deletions in exon 19 and point mutations in exon 21. Cases with classical EGFR mutations show a good response to EGFR tyrosine kinase inhibitors (TKIs), the standard first-line treatment. With the development of next generation sequencing, some uncommon genomic mutations have been detected. However, the effect of TKIs on such uncommon EGFR mutations remains unclear.

CASE SUMMARY
Here, we report a case of rare EGFR co-mutation in non-small cell lung cancer and the efficacy of afatinib on this EGFR co-mutation. A 64-year-old woman was diagnosed with thoracolumbar and bilateral local rib bone metastases, bilateral pulmonary nodules, and pericardial and left pleural effusion. The pathological diagnosis was lung adenocarcinoma. To seek potential therapeutic regimens, rare co-mutation comprising rare EGFR G724S/R776H mutations and amplification were identified. The patient experienced a significant clinical response with a progression-free survival of 17 mo.

CONCLUSION

Key Words: EGFR G724S and R776H; Afatinib; Non-small cell lung cancer; Case report
Non-small cell lung cancer (NSCLC) is the leading cause of cancer death, especially in developing countries such as China\(^1\). A recent study shows that in 2015 there were about 733000 newly diagnosed cases of NSCLC in China, with approximately 610000 Chinese patients dying from the disease\(^2\). NSCLC accounts for the majority (75%) of clinical lung cancer cases. Adenocarcinoma is the most common histological type of NSCLC and can be subdivided into different clinically relevant molecular subtypes according to the type of driver gene mutation.

**EGFR** was the first identified targetable oncogenic driver discovered in NSCLC\(^3\). Approximately 40% of Asian patients with newly diagnosed metastatic NSCLC harbor a somatic mutation in the **EGFR** gene\(^4\). The most common **EGFR** mutations are in-frame deletions in exon 19 and point mutations in exon 21. However, rare mutations were found in nearly 10%-15% of **EGFR**-positive NSCLC and NSCLC with rare mutations had significantly different responses to **EGFR** tyrosine kinase inhibitor. Herein, we describe a rare case of rare **EGFR** G724S/R776H mutations and amplification in a NSCLC responding to afatinib.

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**INTRODUCTION**

CASE PRESENTATION

**Chief complaints**

A 64-year-old nonsmoking woman visited our hospital on April 26, 2019 for further treatment because she could not tolerate the side effects of previous chemotherapy for lung adenocarcinoma, including myelosuppression and cardiac and renal insufficiency.

**History of present illness**

Chest computed tomography (CT) showed bone metastases in the thoracolumbar spine and bilateral local ribs, nodules in both lungs, and pericardial and left pleural effusion.

**History of past illness**

On September 10, 2014, the patient went to a local hospital because of sudden glossolalia with right lower limb numbness, and was diagnosed with stage IIIA lung adenocarcinoma, and then she underwent resection of the upper lobe on September 24, 2014 (Figure 1A). The patient received pemetrexed combined with carboplatin for four cycles of chemotherapy. In November 2015, the disease progressed. The patient was given paclitaxel plus cisplatin combined with bevacizumab for six cycles from November 11, 2015 to March 11, 2016. From April 1, 2016 to April 26, 2019, the patient received pemetrexed combined with bevacizumab, and his condition remained stable.
**Figure 1 Diagnosis and treatment of the patient’s disease.** A: Treatment of lung adenocarcinoma using different regimens; B: Imaging diagnosis during pemetrexed plus bevacizumab treatment; C: Imaging diagnosis before afatinib therapy; D: Pathological diagnosis.

(Figure 1B). After the last cycle of treatment with pemetrexed plus bevacizumab, chest CT showed bone metastases in the thoracolumbar spine and bilateral local ribs, nodules in both lungs, and pericardial and left pleural effusion (Figure 1C).

**Laboratory examinations**
The previous pathological diagnosis was lung adenocarcinoma (Figure 1D).

**Imaging examinations**
After the last cycle of treatment with pemetrexed plus bevacizumab, CT showed bone metastases in the thoracolumbar spine and bilateral local ribs, nodules in both lungs, and pericardial and left pleural effusion (Figure 1C).

**FINAL DIAGNOSIS**
Because the patient could not tolerate the side effects of chemotherapy, potential therapeutic regimens were sought. Her blood was subjected to NGS analysis, and a rare EGFR G724S [mutant allele frequency (MAF): 67.59%] mutation in exon 18 and R776H (MAF: 40.54%) mutation in exon 20 as well as amplification was identified (Figure 2). Therefore, the patient was finally diagnosed with lung adenocarcinoma with rare EGFR G724S and R776H mutations and amplification.

**TREATMENT**
Based on the above findings, the patient was administered with afatinib (30 mg qd) combined with bevacizumab and followed regularly.
OUTCOME AND FOLLOW-UP

After 4 mo of treatment, the left pleural effusion and pericardial effusion were significantly reduced and the patient showed SD according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (Figure 3). The MAFs for both R776H and G724S were also decreased (R776H from 40.54% to 0.16% and G724S from 67.59% to undetected). During this period, zoledronic acid was irregularly given for anti-bone metastasis therapy. The patient was followed several times, and CT performed on July 10, 2020 showed that the tumor lesion of the right lung remained stable (Figure 3). However, the reexamination on October 25, 2020 revealed disease progression with multiple bone metastases (Figure 4). Imaging studies indicated progressive disease (PD), and the patient's final PFS was 17 mo. There were no obvious adverse reactions during the treatment.

DISCUSSION

In the era of precision medicine, EGFR genotyping has become the standard practice for NSCLC, but the identification of rare mutations does not necessarily imply clear targeted therapeutic action. Due to the small number and high heterogeneity of patients with rare mutations, the efficacy of EGFR TKIs in patients with rare EGFR mutations remains unclear. However, a large number of clinical studies have shown significant differences in the efficacy of EGFR TKIs in patients with rare mutations in
Figure 3 The patient's clinical course including treatment history and relevant imaging studies. A: At baseline before therapy with afatinib combined with bevacizumab; B: At 4 mo of therapy with afatinib combined with bevacizumab, with an SD response; C: At 14 mo of therapy with afatinib combined with bevacizumab, with an SD response. D: At 17 mo of therapy with afatinib combined with bevacizumab, with a progressive disease response.

As a second-generation EGFR TKI, afatinib is more effective than chemotherapies and first-generation EGFR-TKIs\[^{8,9}\]. In LUX-Lung 7 and LUX-Lung 8 studies, it was found that patients treated with afatinib as both first-line treatment (compared with gefitinib) and second-line treatment (compared with erlotinib) resulted in a longer PFS or OS\[^{10,11}\]. However, most patients with rare or complex EGFR mutations had a shorter PFS than patients with exon 19 deletion (16.0 mo vs 9.0 mo; HR, 0.34; 95% CI, 0.13-0.94, \( P = 0.037 \))\[^{12}\]. In addition, it has been reported that patients aged ≥ 65 years with rare mutations have significantly longer PFS than patients aged < 65 years after receiving EGFR TKIs (median PFS: 10.5 mo vs 5.5 mo, \( P = 0.0320 \))\[^{13}\]. Patients with rare EGFR mutations are often excluded from clinical trials. However, these adverse characteristics are frequently encountered in clinical practice, and in particular, rare mutations of EGFR (two or more EGFR mutations at the same time) are generally considered a relatively rare event representing a unique and highly heterogeneous subset of NSCLC.

CONCLUSION

In summary, we report a rare case of NSCLC with EGFR G724S/R776H and amplification, which has never been reported before. The successful use of afatinib in this case may provide a new treatment option for this type of EGFR co-mutation, especially for patients who decline or are not suitable for chemotherapy. By deepening our understanding of functional and structural differences between rare subtypes of EGFR variation, the different responses to EGFR TKIs and overall survival rates of patients with these mutations need to be further studied. This case provides valuable insights for future clinical cancer treatment.
Figure 4 Diagnosis of disease progression in the patient. Whole-body bone scan and organ tomography revealed increased uptake of multiple imaging agents in the skull, spine, ribs on both sides, pelvis composition, and upper left femur, suggesting bone metastasis of the tumor.

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